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(54) Title: USES OF OXANDROLONE

(57) Abstract

The subject invention provides many new pharmaceutical uses of oxandrolone, including a method of ameliorating inflammation in a patient suffering from a disorder causing inflammation which comprises administering an oxandrolone to the patient.

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USES OF OXANDROLONE

This application claims priority of U.S. Provisional Application Serial Nos. 60/033,166 and 60/032,415, both filed December 5, 1996, the contents of which are hereby incorporated into this application by reference. Throughout this specification, various publications are referenced by Arabic numerals within parentheses. Full citations for these references may be found at the end of the specification immediately preceding the claims. The disclosure of these publications in their entireties are hereby incorporated by reference into this specification in order to more fully describe the state of the art to which this invention pertains.

Background of the Invention

Oxandrolone

Oxandrolone (17-methyl-17-hydroxy-2-oxa-5-androstan-3-one) is a known compound which is commercially available. The preparation of oxandrolone is described, *inter alia*, in U.S. Patent No. 3,128,283. Oxandrolone is an anabolic steroid synthetically derived from testosterone. Oxandrolone has a unique chemical structure compared with other testosterone analogs. Oxandrolone contains an oxygen rather than a carbon atom at the 2-position within the phenanthrene nucleus (2) and lacks a 4-ene function in the A-ring. The anabolic activity of oxandrolone is approximately 6 times greater than its androgenic activity and has been found to be 6.3 times greater than that of methyltestosterone (2).

Anabolic activity refers to the ability to cause nitrogen retention, promoting weight gain and increasing muscle strength. Androgenic activity refers to the ability to enhance male characteristics (i.e. secondary sex

characteristics such as facial hairs and voice changes). Because of the high ratio of anabolic to androgenic activity, oxandrolone is less likely to cause adverse cosmetic consequences in women than many testosterone analogs.

Furthermore, in contrast to the majority of oral androgenic anabolic steroids (e.g. micronized testosterone, methyltestosterone, fluoxymesterone), oxandrolone undergoes relatively little hepatic metabolism (3, 4).

Oxandrolone has been administered to malnourished patients with alcoholic hepatitis (5, 6). Oxandrolone has been shown to be safe even in dosages of up to 80 mg/day in patients with alcoholic hepatitis (5).

The subject invention discloses new uses of oxandrolone.

Summary of the Invention

The subject invention provides many new pharmaceutical uses of oxandrolone, including a method of ameliorating inflammation in a patient suffering from a disorder causing inflammation which comprises administering an oxandrolone to the patient.

Detailed Description of the Invention

Oxandrolone as used herein encompasses 17-methyl-17-hydroxy-2-oxa-5-androstan-3-one (both racemic mixtures and optically active enantiomers) as well as pharmaceutically acceptable esters thereof. For example, an oxandrolone product which is commercially available is the Oxandrin® tablet from BTG Pharmaceuticals Corp., Iselin, NJ 08830, which is 17α-methyl-17β-hydroxy-2-oxa-5α-androstan-3-one. This product was used throughout the studies described herein.

Oxandrolone may be administered orally, intravenously, intramuscularly, subcutaneously, topically, intratracheally, intrathecally, intraperitoneally, rectally, vaginally or intrapleurally.

If oxandrolone is administered orally, it is administered in the form of a tablet, a pill, a liquid or a capsule.

A liquid may be administered in the form of a solution or a suspension.

The compositions produced in accordance with the invention may comprise conventional pharmaceutically acceptable diluents or carriers. Tablets, pills, liquids and capsules may include conventional excipients such as lactose, starch, cellulose derivatives, hydroxypropyl methylcellulose and magnesium stearate. Suppositories may include excipients such as waxes and glycerol. Injectable solutions will comprise sterile pyrogen-free media such as saline and may include buffering agents, stabilizing agents, solubilizing agents or preservatives. Conventional enteric coatings may also be used.

Compositions for topical administration may be in the form of creams, ointments, lotions, solutions, transdermal delivery systems, transdermal patches or gels.

Oxandrolone may be administered in a solid dosage form, in a liquid dosage form, in a sustained-release formulation or in a once a day formulation. The liquid dosage form may inter alia be alcohol-based or formulated with a cyclodextrin such as hydroxypropyl-β-cyclodextrin.

Weight loss in patients with congestive heart failure (CHF) is commonly referred to as cardiac cachexia. The prevalence of CHF is estimated to be 1.1-2% of adults in the United States. Cachexia is a consistent finding in chronic CHF. Correcting or minimizing the wasting associated with heart failure may offer important benefits in the treatment of the condition (1).

CHF can be caused by cardiomyopathy, heart failure, hypertension, and so on.

Cardiomyopathy is a term used to describe heart muscle disease and encompasses dilated (congestive) cardiomyopathy, hypertrophic (obstructive) cardiomyopathy and restrictive cardiomyopathy.

Hypertension as used herein encompasses a higher than normal blood pressure. Normal blood pressure as used herein is a systolic pressure below 140mmHg together with a diastolic pressure below 90mmHG.

Heart failure as used herein encompasses acute or chronic heart failure. Chronic heart failure is a consequence of cardiac abnormality, injury or cardiovascular stress. Chronic heart failure can be caused by myocardial infarction, cardiomyopathy, cor pulmonale, hypertension, valvular heart disease, infections, cardiotoxicity from alcoholism or induced by drugs, chronic severe anaemia or hyperthyroidism.

Infertility in men is characterized by the inability of sperm produced by such men to fertilize the ovum. Sub-

fertility in men is characterized by poor or insufficient semen quality. Sterility in men is characterized by the lack of sperm production.

Bone disease as used herein encompasses any bone disorder such as osteogenesis imperfecta, osteoporosis, osteomalacia, Paget's disease of bone, and renal osteodystrophy. Osteoporosis is a disorder of low bone mass. Renal osteodystrophy is a complex condition associated with chronic renal failure which involves the development of hyperparathyroid bone disease and osteomalacia (impaired mineralization of the bone matrix resulting in "soft" bones).

Cancer as used herein encompasses any form of cancer such as carcinoma, sarcoma, leukemia, adenoma, lymphoma, myeloma, blastoma, seminoma and melanoma.

Bone marrow depression as used herein encompasses hypoplastic (aplastic) anemia. Aplastic anemia can be caused by a chemical agent, radiation, drugs, infection, chemotherapy, radiotherapy, radiation or an inflammatory event.

Renal failure as used herein encompasses acute and chronic renal failure. Acute renal failure is associated with rapid steadily increasing azotemia with or without oliguria. Chronic renal failure results from a multitude of pathological processes that lead to derangement and insufficiency of renal excretory and regulatory function (uremia).

Obesity as used herein encompasses an increase in body weight of more than 20% than normal due to an excessive accumulation of fat in the body. It occurs when there is an imbalance between energy intake and energy expenditure.

Thyroid failure as used herein encompasses hyperthyroidism

and hypothyroidism.

Head injury as used herein encompasses damage resulting from the penetration of the skull or from rapid acceleration or deccelaration of the brain, which injures tissue at the point of impact at its opposite pole (contrecoup) and also diffusely along the frontal and temporal lobes.

The subject invention provides a method of treating involuntary weight loss associated with congestive heart failure in a patient suffering from congestive heart failure which comprises administering an oxandrolone to the patient.

In a preferred embodiment, the oxandrolone is administered in a therapeutically effective amount.

The subject invention also provides a method of improving heart muscle function in a patient suffering from congestive heart failure which comprises administering an oxandrolone to the patient.

Congestive heart failure may be caused by cardiomyopathy, heart failure, hypertension and other causes.

The subject invention further provides a method of treating a patient by surgery or chemotherapy or radiotherapy wherein prior to the surgery or the chemotherapy or the radiotherapy, the patient is administered an oxandrolone.

The subject invention envisages a method of stimulating the immune system in a patient suffering from immunosuppression which comprises administering an oxandrolone to the patient.

The immunosuppression may for example be caused by bone marrow depression or severe injury.

Bone marrow depression may for example be caused by chemotherapy or radiotheraphy and severe trauma may for

example be a head injury.

The subject invention also provides a method of treating a male patient suffering from infertility or sub-fertility which comprises administering an oxandrolone to the patient.

The subject invention additionally provides a method of promoting cartilage repair in a patient which comprises administering an oxandrolone to the patient.

The subject invention envisages a method of regenerating bone in a patient suffering from a bone disease which comprises administering an oxandrolone to the patient.

In a preferred embodiment bone disease is osteoporosis or renal osteodystrophy.

The subject invention further provides a method of treating a symptom associated with cancer in a patient suffering from cancer which comprises administering an oxandrolone to the patient.

The subject invention further envisages a method of treating a symptom associated with renal failure in a patient suffering from renal failure which comprises administering an oxandrolone to the patient.

In a preferred embodiment, the patient suffering from the renal failure is a dialysis patient.

The subject invention further envisages a method of treating a symptom associated with thyroid failure in a patient suffering from thyroid failure which comprises administering an oxandrolone to the patient.

The subject invention provides a method of treating obesity in a patient suffering from obesity which comprises administering an oxandrolone to the patient.

The subject invention further provides a use of an oxandrolone in the preparation of a composition to treat any of the above mentioned diseases or disorders.

An example of intestinal inflammation is inflammatory bowel disease.

Inflammatory bowel disease as used herein encompasses chronic non-specific inflammatory conditions of the gastro-intestinal tract. Two major forms of inflammatory bowel disease are Crohn's disease and ulcerative colitis.

Diarrhea as used herein is characterized by liquid stools, increased stool weight and frequency of defaecation. Diarrhea as used herein may be caused by any infection (bacterial, viral or protozoal), by accumulation of nonabsorbed osmotically-active solutes in the gastrointestinal lumen (as for example in lactase deficiency), by gastrointestinal effects of secretory stimuli, or by diseases where intestinal motility or morphology is altered (as for example in irritable bowel syndrome).

Arthritis as used herein encompasses any form of arthritis such as rheumatoid arthritis. Rheumatoid arthritis is a chronic systemic inflammatory disease which mainly affects the synovial joints.

The subject invention provides a method of ameliorating inflammation in a patient suffering from a disorder causing inflammation which comprises administering a therapeutically effective amount of an oxandrolone to the patient.

The disorder causing inflammation may be intestinal inflammation, inflammatory bowel disease, arthritis, synovial inflammation or any disorder which causes inflammation including, but not limited to, systemic inflammatory syndrome, septic shock generated by gram or

gram$^+$ bacteria, endotoxin (LPS)-induced inflammation, trauma or any condition in which interleukins are released and systemic shock effects are produced.

Lung fibrosis may result from inflammation caused for example by a neoplastic agent such as bleomycin.

The subject invention further provides a method of treating diarrhea in a patient suffering from diarrhea which comprises administering an oxandrolone to the patient.

The invention also provides a method of treating short bowel syndrome in a patient suffering from short bowel syndrome which comprises administering an oxandrolone to the patient.

Oxandrolone may be administered in a solid dosage form, in a liquid dosage form, in a sustained-release formulation or in a once a day formulation. The liquid dosage form may inter alia be alcohol-based or formulated with a cyclodextrin such as hydroxypropyl-β-cyclodextrin.

The subject invention also provides a method of ameliorating inflammation caused by an auto-immune disease which comprises administering an oxandrolone to the patient.

The subject invention also provides a method of preserving the gut lining in a patient suffering from intestinal inflammation which comprises administering an oxandrolone to the patient.

The subject invention also envisages a use of an oxandrolone in the preparation of a composition to ameliorate inflammation in a patient suffering from a disorder causing inflammation.

The subject invention further provides a composition for use in topical treatment of inflammation comprising an oxandrolone and a pharmaceutically acceptable carrier.

Oxandrolone may be used prophylactically to prevent recurring of symptoms in a patient suffering from a disorder causing inflammation.

Interferon as used herein encompasses any interferon such as alpha-interferon, beta-interferon or gamma-interferon.

Corticosteroid as used herein encompasses inter alia glucocorticoids, mineralcorticoids and androgens. Examples of glucocorticoids are hydrocortisone, cortisone, corticosterone and synthetic analogs of hydrocortisone and cortisone (such as cortisol, prednisolone and prednisone). Examples of mineralcorticoids are aldosterone and desoxycorticosterone. Examples of androgens are DHEA, androstenedione, testosterone and 11β-hydroxyandrostenedione.

The oxandrolone may be administered in conjunction with a corticosteroid, an interferon or any known anti-inflammatory agent.

Oxandrolone may also be administered in conjunction with glutamine or human growth hormone.

Oxandrolone may be substituted for testosterone in male patients suffering from low testosterone levels where testosterone treatment is not acceptable or inappropriate (testosterone replacement therapy). An example of such a patient is an elderly man with prostate cancer.

Examples

The Examples which follow are set forth to aid in understanding the invention but are not intended to, and should not be construed to, limit its scope in any way.

EXAMPLE 1: The effect of oxandrolone on inflammation

The rat model of carrageenan-induced paw edema is used to assay the anti-inflammatory activity of oxandrolone. In this model, rats are given a sub-plantar injection of carrageenan into the left hind paw. The paw volume is measured by a Hg-displacement volumeter before and at hourly intervals after paw injection. Rats are divided into three groups. One group receives a subcutaneous injection of oxandrolone long before carrageenan administration. A second group receives a subcutaneous injection of oxandrolone closer to carrageenan administration. The other group does not receive any pretreatment and serves as a control.

The swelling response is reduced indicating efficacy of oxandrolone as an anti-inflammatory agent.

EXAMPLE 2: The effect of oxandrolone on Synovial Inflammation

As a model for synovial inflammation and the ability of oxandrolone to inhibit such inflammation, the knee-joint (synovial) inflammation model in rats is utilized. (Ginsburg et al., in "Bayer-Symposium VI: Experimental Models of Chronic Inflammatory Diseases", 256-299, 1977, Springer-Verlag).

In this model, inflammation is induced by intraarticular injection of bacterial lipopolysaccharide endotoxin (LPS). The degree of inflammation is reflected by the swelling of the synovial tissue and is measured as the increase in weight postadministration. The LPS toxin and oxandrolone are co-administered.

The LPS-induced synovial inflammation is inhibited which indicates efficacy of oxandrolone as an inhibitor of synovial inflammation.

EXAMPLE 3: The effect of Oxandrolone on Adjuvant-Induced Arthritis

The induction of joint inflammation in rats by administration of Freund's adjuvant is considered to be the model of choice for experimental rheumatoid arthritis (Newbould (1963), Brit. J. Pharmacol. 21: 127). An injection of the adjuvant (Freund's adjuvant with killed Mycobacterium Tuberculosis) into the foot pad results in an initial swelling of the paw, reaching a plateau after 3 days, followed after 14 days by a second increase in paw and joint swelling, which persists for another 7-10 days. The second phase is regarded as the phase of immunologically-induced chronic arthritis. To examine the efficacy of oxandrolone as an anti-arthritic drug, oxandrolone is given subcutaneously (in doses expressed as mg per kg body weight) to adjuvant-treated rats during 14-21 days after adjuvant administration. Oxandrolone is given daily or on alternating days. As a negative control, saline is given subcutaneously to a second group of adjuvant-treated rats.

Joint inflammation is reduced which indicates efficacy of oxandrolone as an inhibitor of arthritis.

EXAMPLE 4: The effect of Oxandrolone on Lung Fibrosis

Bleomycin (BLM) is an antineoplastic agent widely used against various types of carcinomas and lymphomas (Counts et al. (1981), J. Pharmacol. Exp. Ther. 219, 675-678). A major problem associated with the use of bleomycin is the induction of lung fibrosis resulting from high doses of the agent, thus limiting its therapeutic usefulness (Crooks and Bradner (1976), J. Med. 7, 333). To examine the possible use of oxandrolone for the protection of the lung from bleomycin-induced fibrosis, the rat model is used as a biological model (Kelley et al. (1980), J. Lab. Clin. Med. 96, 254). In this model, rats are treated with bleomycin given intra-tracheally. A second group of rats, the negative control, receives saline only, while a third group receives bleomycin as group 1 and is then treated with oxandrolone.

The lungs of the surviving rats are excised and the collagen content (expressed as hydroxy-proline content) is determined (using standard procedures according to Woessner in "The methodology of Connective Tissue Re-search", Hall, Ed. Oxford (1976), Joynson-Bruvvers Ltd., 227-233 and Woessner (1961), Arch. Biochem. Biophys. 93, 440-447). The lung weights are determined (normalized for 100 gram body weight).

In additional experiments, the effects of frequency as well as different routes of administration may be researched.

In experiments, oxandrolone is given subcutaneously either once every other day or by a single injection on Day 1 or by using an intraperitoneal route of administration rather than a subcutaneous route.

Lung fibrosis is reduced which indicates efficacy of oxandrolone as a treatment for lung fibrosis.

References

1. Freeman et al. (1994), Nutrition reviews 52(10): 340-347.

2. Fox et al. (1962), J. Clin. Endocrinol. Metab. 22: 921-924.

3. Karim et al. (1973), Clin. Pharmacol. Therap. 14: 862-869.

4. Masse et al. (1989), Biomedical and Environmental Mass Spectrometry 18:429-438.

5. Mendenhall et al. (1993), Hematology 17(4): 564-576.

6. Bonkovsky et al. (1991), The American Journal of Gastroenterology 86(9): 1209-1218.

What is claimed is:

1. A method of treating involuntary weight loss associated with congestive heart failure in a patient suffering from congestive heart failure which comprises administering an oxandrolone to the patient.

2. A method of improving heart muscle function in a patient suffering from congestive heart failure which comprises administering an oxandrolone to the patient.

3. A method according to claims 1 or 2 wherein the congestive heart failure is caused by cardiomyopathy.

4. A method according to claims 1 or 2 wherein the congestive heart failure is caused by heart failure.

5. A method according to claims 1 or 2, wherein the congestive heart failure is caused by hypertension.

6. A method of treating a patient by surgery or chemotherapy or radiotherapy wherein prior to the surgery or chemotherapy or radiotherapy, the patient is administered an oxandrolone.

7. A method of stimulating the immune system in a patient suffering from immunosuppression which comprises administering an oxandrolone to the patient.

8. A method according to claim 7 wherein the immunosuppression is caused by bone marrow depression.

9. A method according to claim 8 wherein the bone marrow depression is caused by chemotherapy or radiotheraphy.

10. A method according to claim 7 wherein the immunosuppression is caused by severe trauma.

11. A method according to claim 10 wherein the severe trauma is a head injury.

12. A method of treating a symptom associated with cancer in a patient suffering from cancer which comprises administering an oxandrolone to the patient.

13. A method of treating a symptom associated with renal failure in a patient suffering from renal failure which comprises administering an oxandrolone to the patient.

14. A method according to claim 13 wherein the patient is a dialysis patient.

15. A method of treating a symptom associated with thyroid failure in a patient suffering from thyroid failure which comprises administering an oxandrolone to the patient.

16. A method of treating obesity in a patient suffering from obesity which comprises administering an oxandrolone to the patient.

17. A method of treating a male patient suffering from low testosterone levels which comprises administering an oxandrolone to the patient.

18. A method according to claim 17 wherein the male patient additionally suffers from prostate cancer.

19. A method according to claims 1, 2, 6, 7, 12, 13, 15, 16 or 17 wherein the oxandrolone is 17α-methyl-17β-hydroxy-2-oxa-5α-androstan-3-one.

20. A method of ameliorating inflammation in a patient suffering from a disorder causing inflammation which comprises administering a therapeutically effective

amount of an oxandrolone to the patient.

21. A method according to claim 20, wherein the disorder is selected from the group consisting of intestinal inflammation, inflammatory bowel disease, lung fibrosis, arthritis, synovial inflammation, septic shock, traumatic shock and auto-immune disease.

22. A method of treating diarrhea in a patient suffering from diarrhea which comprises administering an oxandrolone to the patient.

23. A method of treating a symptom in a patient suffering from short bowel syndrome which comprises administering an oxandrolone to the patient.

24. A method according to claims 20, 22 or 23 wherein the oxandrolone is administered orally.

25. A method according to claim 20 wherein the oxandrolone is administered topically.

26. A method according to claims 20, 22 or 23 wherein the oxandrolone is injected.

27. A method according to claims 20, 22 or 23 wherein the oxandrolone is administered in conjunction with a corticosteroid to the patient.

28. A method according to claims 20, 22 or 23 wherein the oxandrolone is administered in conjunction with an interferon to the patient.

29. A composition for use in topical treatment of inflammation which comprises an oxandrolone and a pharmaceutically acceptable carrier.

30. A method according to claims 20, 22 or 23, wherein the oxandrolone is 17α-methyl-17β-hydroxy-2-oxa-5α-androstan-3-one.

31. A composition according to claim 29, wherein the oxandrolone is 17α-methyl-17β-hydroxy-2-oxa-5α-androstan-3-one.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 31/58
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/172

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN, APS
search terms: oxandrolone, thyroid, cardiac, obesity, inflamation.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Lovejoy,J. C. et al. Oral anabolic steroid treatment, but not parenteral androgen treatemnt, decreases abdominal fat in obese, older men, Chemical Abstracts; 18 December 1995 Vol. 123, No.25 pages 145-146,Abstract no.330267Y.	1-31

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

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Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer THEODORE J. CRIARES Telephone No. (703) 308-1235

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(71) Applicant *(for all designated States except US)*: BIO–TECHNOLOGY GENERAL CORP. [US/US]; Metro Park Financial Center, 70 Wood Avenue South, Iselin, NJ 08830 (US).

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CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
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